Session 3: Nickel Leaching

Moderators: Nicole Ibrahim and Jennifer Goode, FDA

- Objective 1: Discuss the consequences of nickel exposure (30 min)
- Objective 2: Discuss in vitro nickel leach testing (60 min)
- Objective 3: Discuss in vitro/in vivo nickel release correlation (60 min)
- Objective 4: Discuss toxicity associated with levels of nickel exposure (60 min)
- Objective 5: Moving Forward: Identify knowledge gaps (30 min)

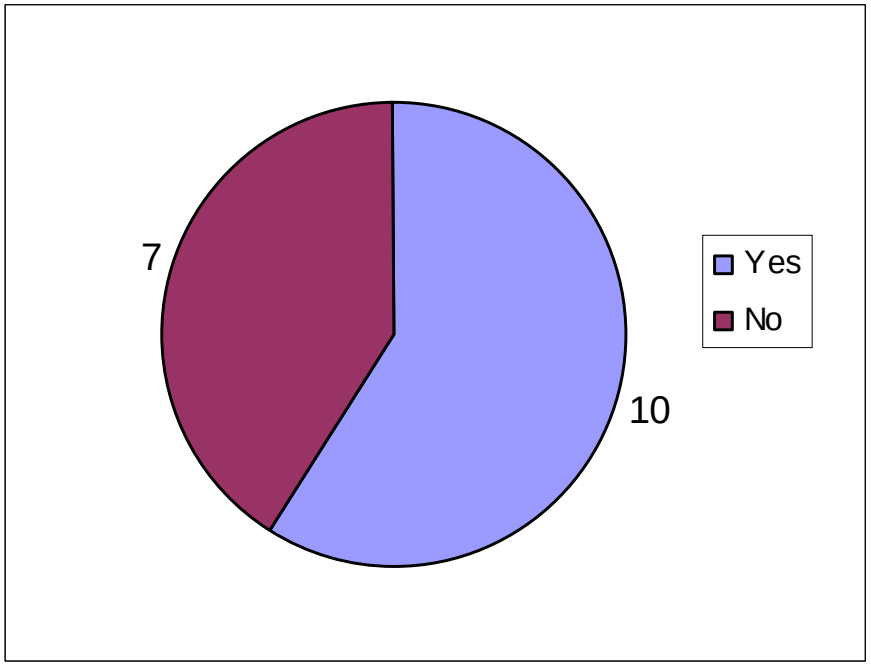
Objective 1: Discuss the biological consequences of nickel exposure (30 min)

- General talk on biological response/toxicity of nickel (Kathy Squibb, University of MD; 20 min)

- Discuss the general biological response to/toxicity of nickel (10 min)

Objective 2: Discuss in vitro nickel leach testing (60 min)

HW: Do you perform in vitro nickel leach testing?



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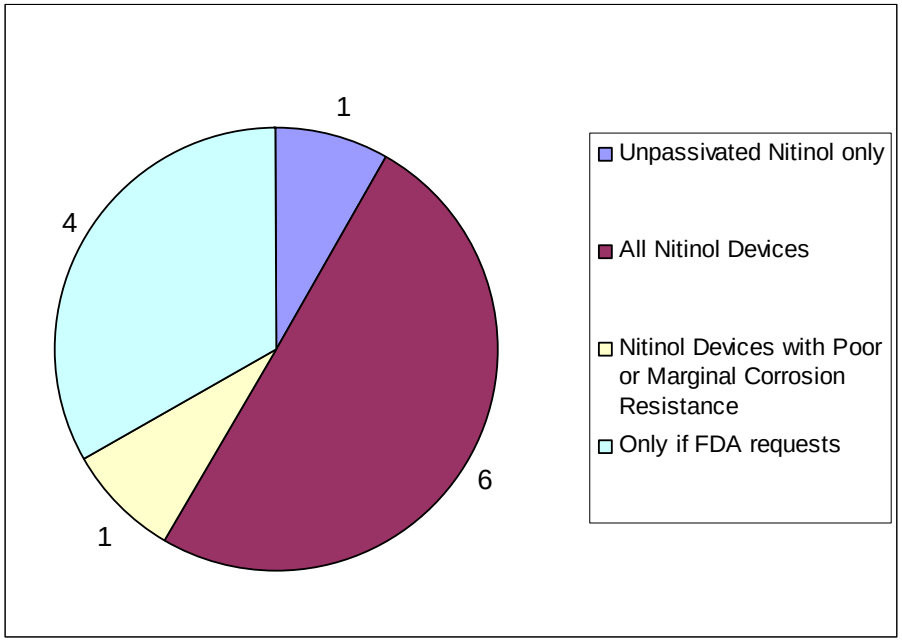
HW: If so, when…..



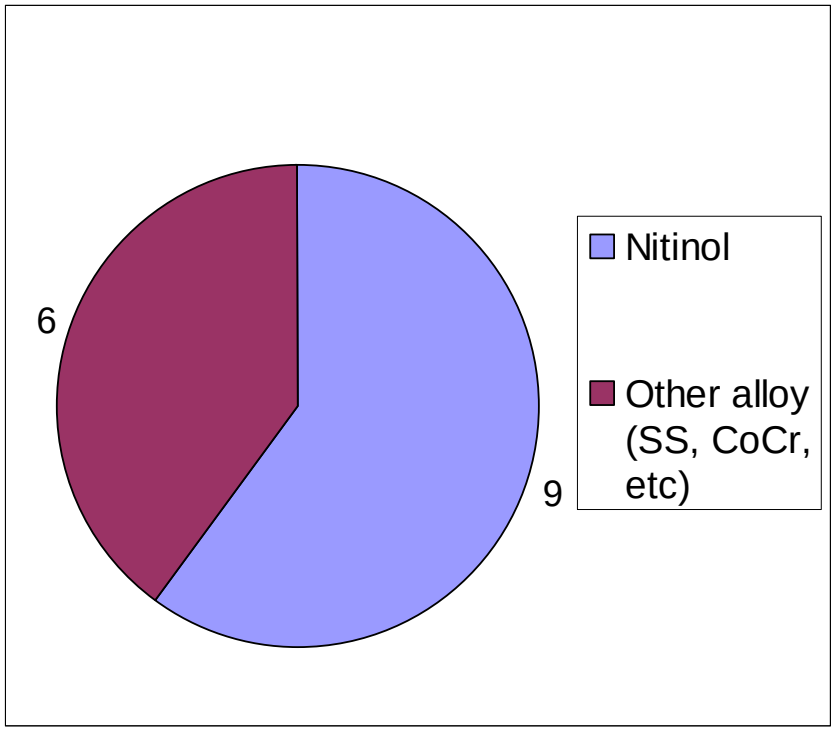
N=8*

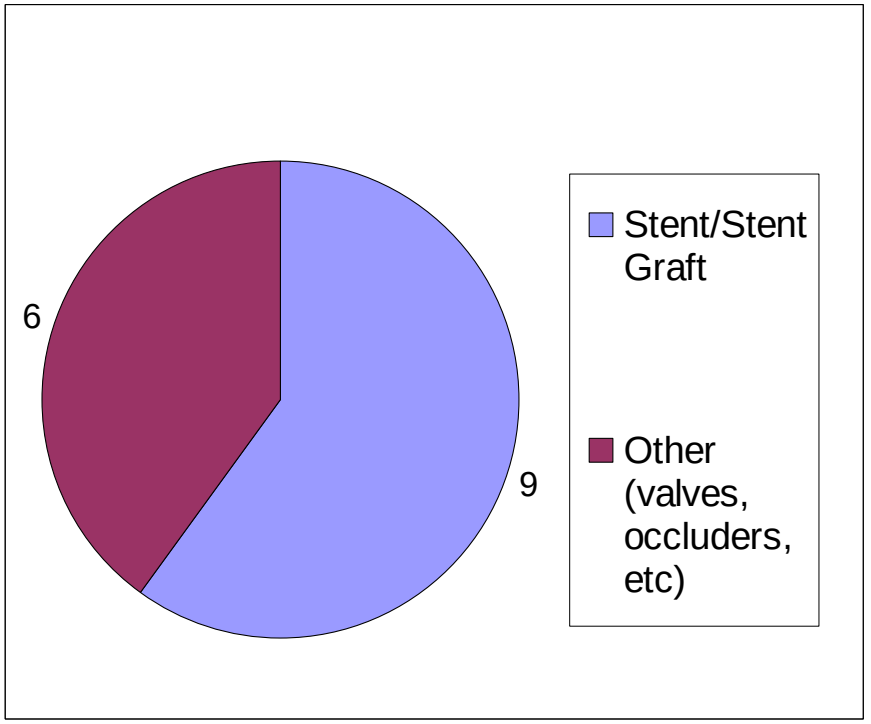
*reflects the option to select multiple scenarios

<u>Categories with no responses</u>:

- All Metallic Devices
- Any Devices with Poor or Marginal Corrosion Resistance
- Nitinol devices with poor fatigue resistance
- Any device with poor fatigue resistance

HW: If you perform nickel leach testing, please indicate the alloy and device type:





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Methods for in vitro nickel leach testing

HW: Please describe the key test parameters you use for in vitro nickel leach testing

Parameters that were consistent across all responses (n=8):

Finished Sterilized Device	Yes
Temperature	37 degrees C
External Mechanical Loading	No
Open Circuit Potential	No*

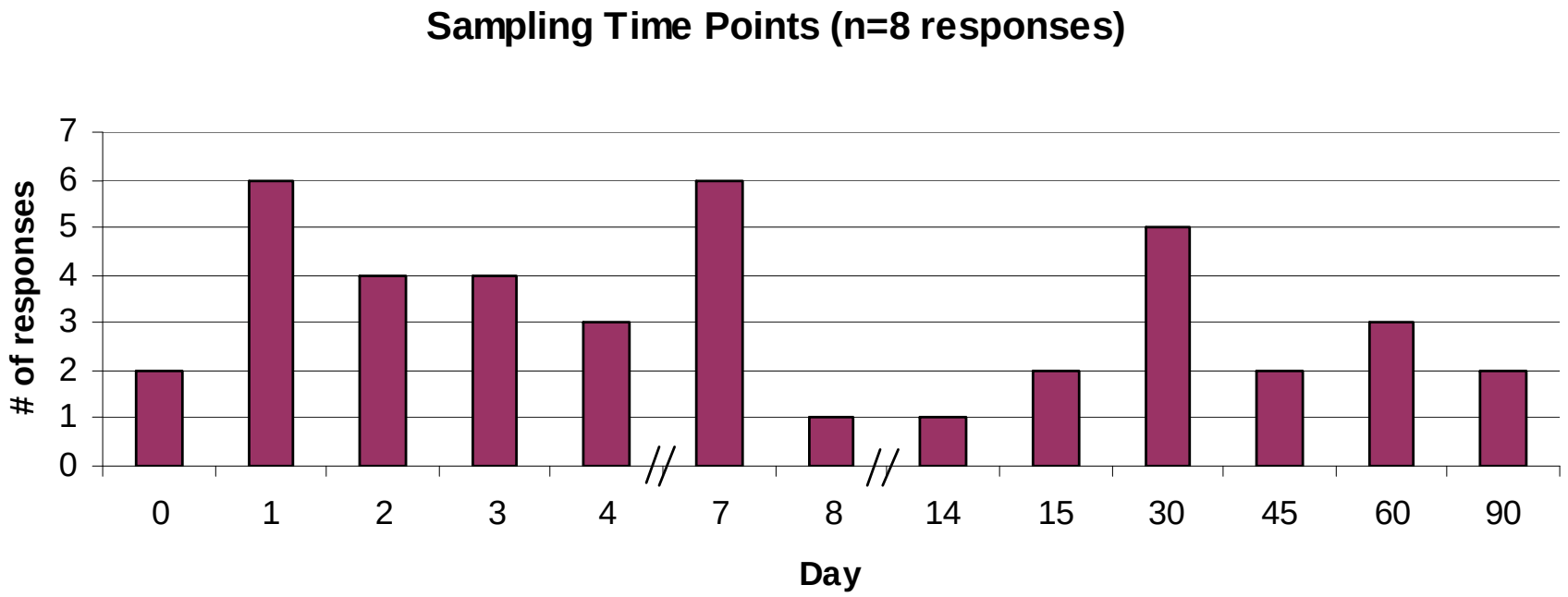
*testing done with or without OCP

HW: Please describe the key test parameters you use for in vitro nickel leach testing

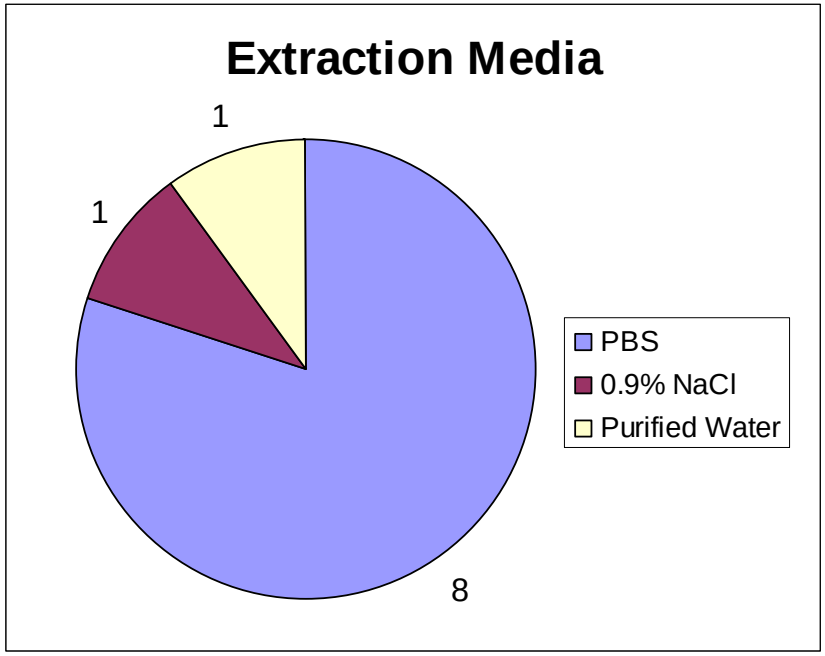
Quantitative Parameters that are varied across all responses

Duration (days; min, max, median) (n=9)	3,90,30
Surface Area Ratio (cm^2/ml; min, max, median) (n=4)	0.1, 6, 0.6
Resolution (μg/ml [ppm]; min, max, median) (n=8)	0.0005, 0.05, 0.00175

HW: Please describe the key test parameters you use for in vitro nickel leach testing



HW: Please describe the key test parameters you use for in vitro nickel leach testing



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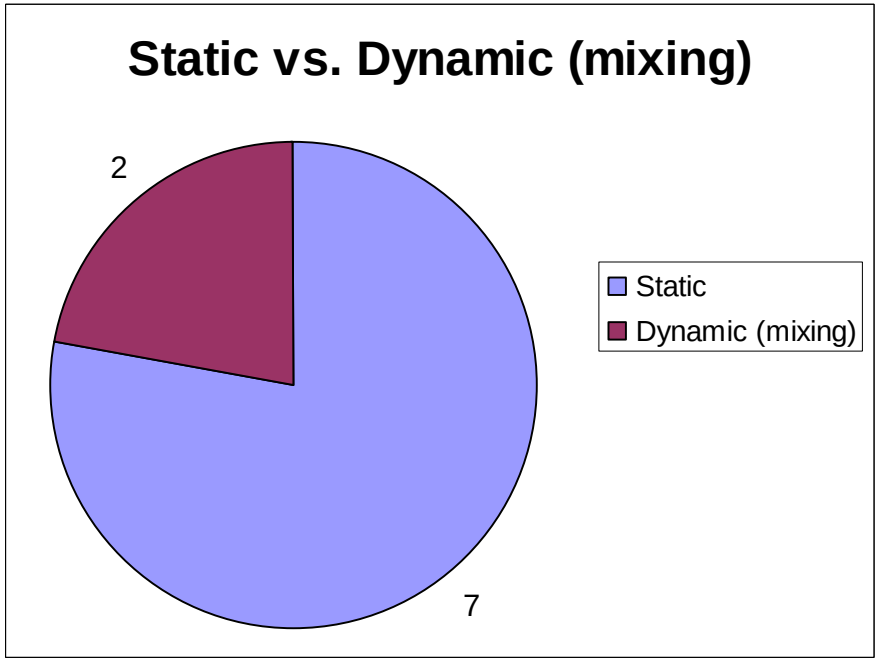

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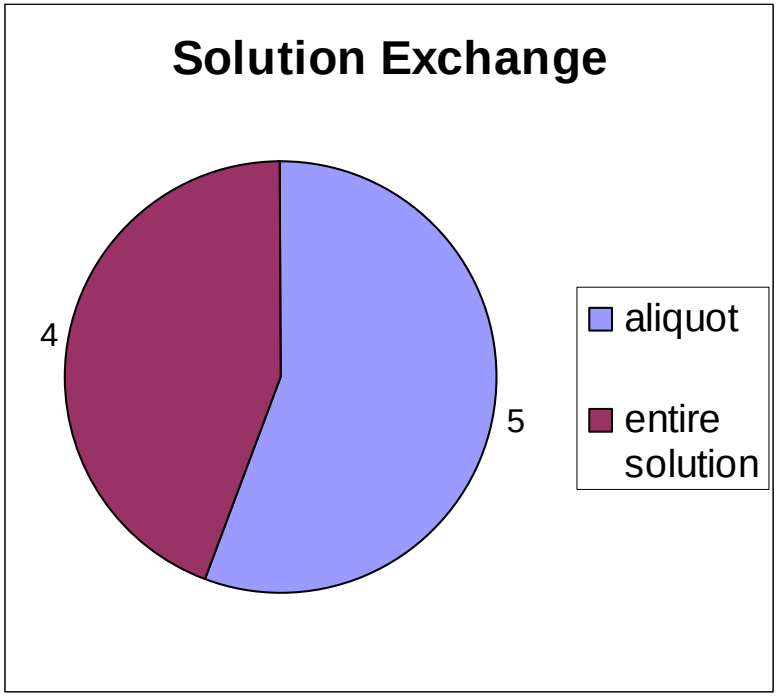
Containers:

- PFE Tubes
- Borosilicate Glass Container
- iChem certified vial
- PFA Containers

HW: Please describe the key test parameters you use for in vitro nickel leach testing



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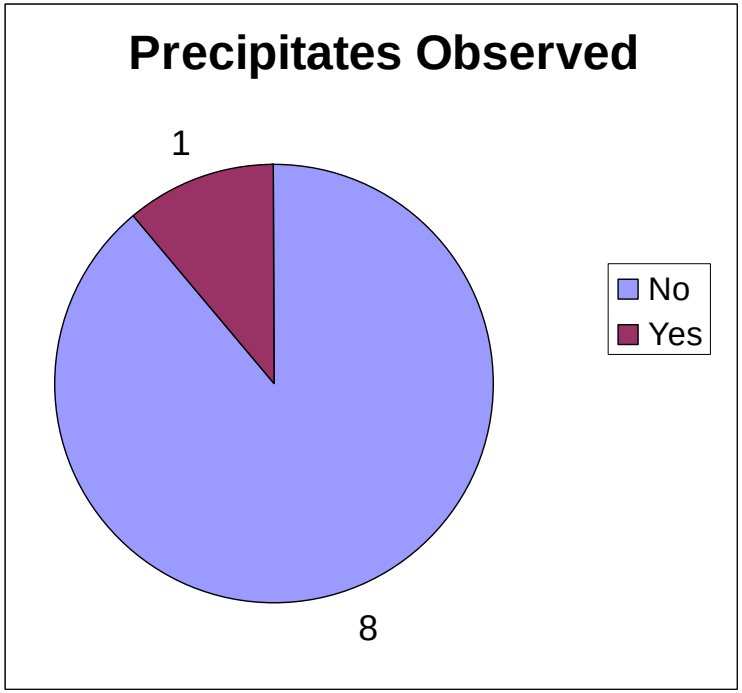

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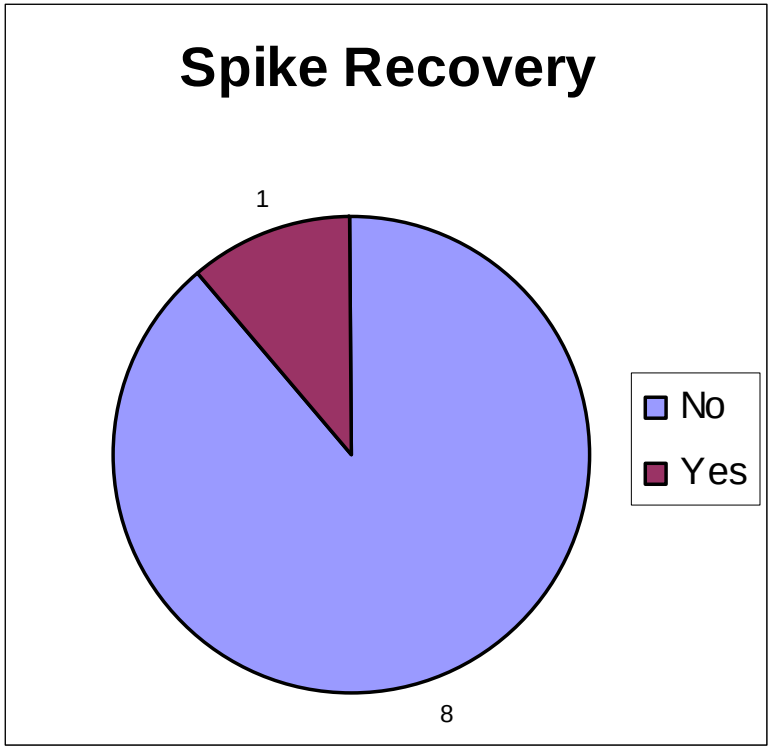
HW: Please describe the key test parameters you use for in vitro nickel leach testing



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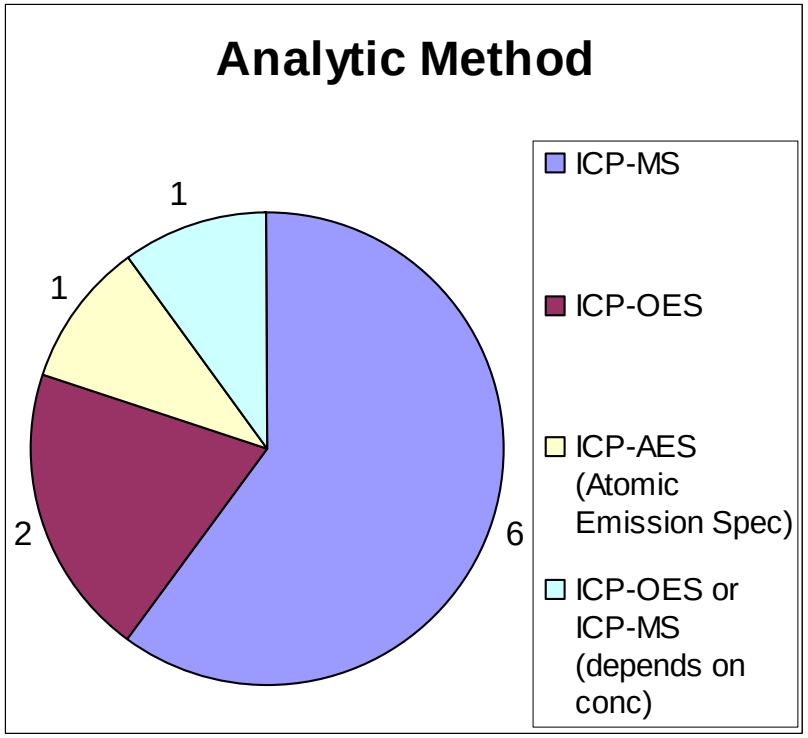

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HW: How much nickel do you typically see being released from your device(s) in vitro?

For nitinol devices:

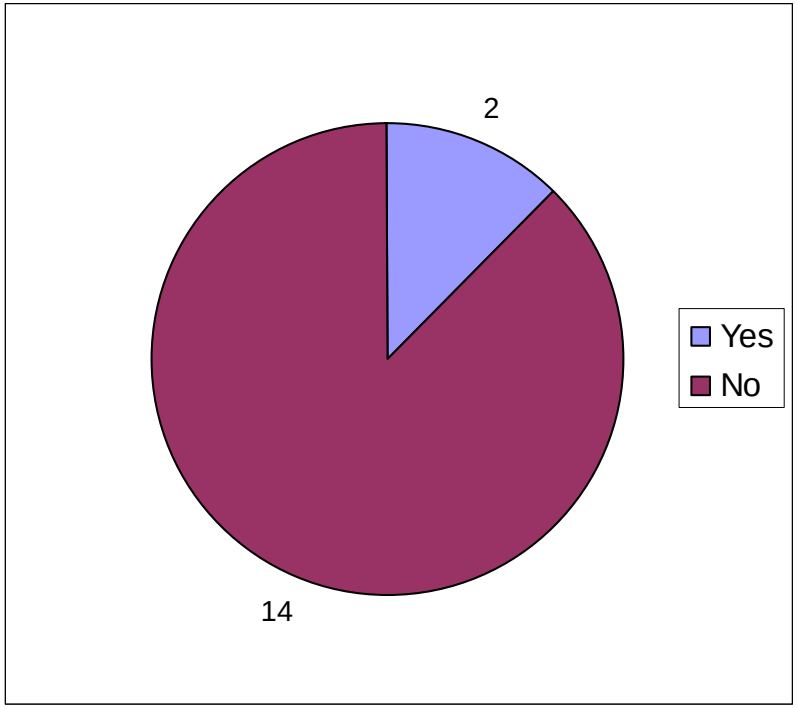
Device Surface Area (min max, median)	0.9, 50.13, 5.3 cm^2	n=8
Minimum peak release rate (range)	0.19-2.89 μg/day	n=5
Maximum Peak release rate (range)	0.42-8.40 μg/day	n=5
Average peak release rate (range)	0.043-4.8 μg/day	n=7
Time to Peak release (min, max, median)	<1, 30, 3.5 days	n=12
Peak release acceptance criteria (range)	35-670 μg/day	n=6
Minimum chronic release rate (range)	<0.015-0.63 μg/day	n=7
Maximum chronic release rate (range)	<0.015-1.72 μg/day	n=7
Average chronic release rate (range)	<0.015-1.31 μg/day	n=7
Minimum Total Release (range)	2.0-80 μg	n=6
Maximum Total Release (range)	5.13-140 μg	n=6
Average Total Release (range)	0.11-110 μg	n=9

Objective 2: Discuss in vitro nickel leach testing

- Discuss best practices (30 min)
  - What are appropriate sampling frequencies and test duration?
  - Does choice of immersion medium matter?
  - How should the possibility of adsorption and precipitation be mitigated?
  - Other?
- Discuss significance of peak vs. total release (10 min)
- Discuss the limitations of in vitro testing (10 min)

Objective 3: Discuss in vitro/in vivo nickel release correlation (60 min)

HW: Do you perform in vivo nickel release assessments ?



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Objective 3: Discuss in vitro – in vivo correlation of nickel release and patient exposure

- Talk on in vivo nickel release in patients with cardiovascular occlusion devices (Joyce Tsuji, Exponent; 20 min)

- Discuss in vivo nickel release in patients (10 min)

Objective 3: Discuss in vivo nickel release assessment

- Discuss what has been learned from in vivo nickel leach testing in literature (10 min)
- Discuss animal and clinical approaches to evaluate nickel release (10 min)
- Discuss the limitations of in vivo nickel assessment (10 min)

Objective 4: Discuss toxicity associated with levels of nickel exposure (60 min)

- Talk on data for toxicity analysis (Ron Brown, FDA; 60 min)

Objective 5: Moving Forward: Identify knowledge gaps (30 min)

- Is the current testing paradigm sufficient to assess nickel release and toxicity?
- What form of nickel is released from medical devices?
- How do you assess nickel toxicity given that there are biological effects of combinations of nickel with other substances?
- Can you extrapolate data and methods from adult populations to develop a pediatric TI?